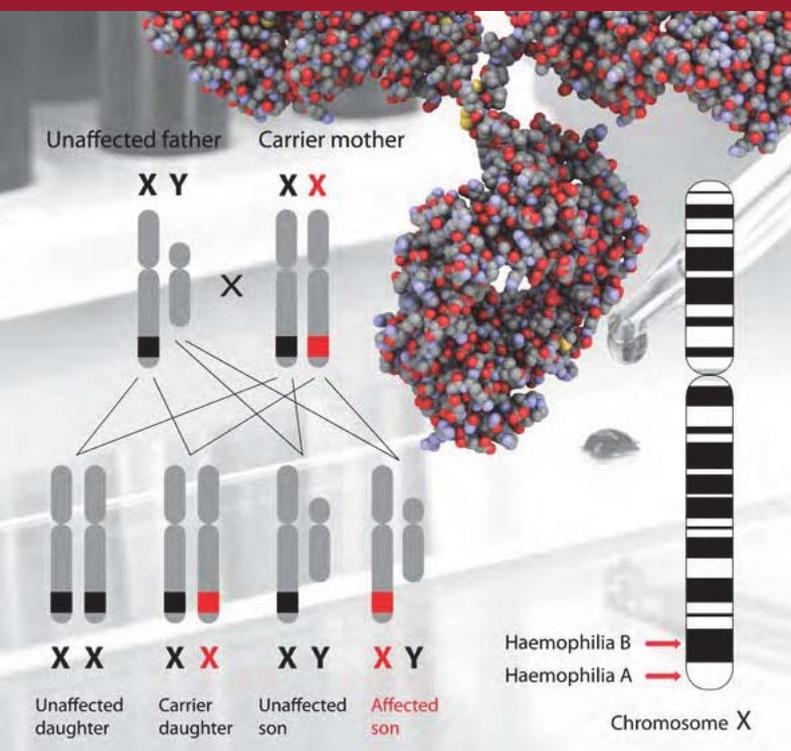


# Optimal use of clotting factors and immunoglobulins



European  
symposium  
proceedings

Wildbad Kreuth  
Germany

European Directorate  
for the Quality of  
Medicines &  
HealthCare

26-27 April 2013

# **Recommendations**

## Working Group 1: Clotting factors

*Moderators:* P.M. Mannucci & Wolfgang Schramm

*Rapporteur:* P. Giangrande

### Summary of discussions:

Several new factor VIII, IX and VIIa concentrates are under development that are essentially copies of existing products. Although the term “biosimilars” is widely used to describe such products, the working group was not entirely satisfied with this term, although no obvious and universally acceptable alternative was agreed upon. It was recognised that these products are effectively in competition with long-acting products for enrollment of patients in clinical trials. For scientific reasons, the latter are generally more attractive to both patients and physicians engaged in clinical trials. However, the working group felt very strongly that biosimilars should not be ignored in favour of new long-acting products. It was also accepted that no “short cuts” should be taken to license biosimilar products, although there certainly is an expectation that these should be significantly cheaper than current products.

On the basis of current data, the working group was enthusiastic about new long-acting factor concentrates under development, particularly for IX, for which a 5-fold extension of half-life has been achieved. It was felt that these novel agents should be used for the treatment of actual bleeds as well as for prophylaxis. At the same time, the unanimous feeling of the working group was that long-acting products would not completely replace the need for current plasma-derived and recombinant concentrates. The principal perceived advantage of long-acting products is the need for fewer infusions, which would be particularly helpful in children, where the need for venous access devices might be avoided. It was also felt that these novel agents could make it easier to individualise therapy and maintain higher trough levels. Peri-operative management would also be easier if fewer infusions are required. Possible disadvantages include concerns about enhanced immunogenicity, thrombogenicity and allergic reactions. A particular issue, for which more data are required, relates to the potential for accumulation of polyethylene glycol (PEG) with repeated administration over many years. The adoption of these products will also create practical problems with regards to assignment of potency and laboratory monitoring in patients. New laboratory standards will be required for assays and indeed some products may eventually be marketed in weight rather than international units. The working group called for pharmaceutical companies to work with the medical community to standardise useful assays. It was accepted that these novel products will be more expensive but, if this drawback is assigned too much weight, then wide-scale adoption in clinical practice will be hindered. As guidance for the representatives of pharmaceutical companies present during this part of the discussions, the working group indicated that a 50% price premium would be considered reasonable; although there would be an expectation that the price of current products would also fall simultaneously.

The working group felt very strongly that decisions on whether to adopt any new product should not be based solely on cost, but also quality. Consensus is required on a model for assessing cost-effectiveness, which should incorporate measurements of quality of life as well as historical control data for comparison.

It was restated that prophylaxis for children with severe haemophilia is recognised as the optimum therapy, as was made clear in recommendations from both the preceding 1999 and 2009 Wildbad Kreuth meetings. There was a strong feeling that the option of on-going prophylaxis for adults should also be considered. Another major recommendation that came

out of the 2009 meeting was that the minimum factor VIII level in a country should be 2 IU/capita. The working group voted to raise this figure to 3 IU/capita in light of data from a recent survey, which indicated that the lower threshold is not sufficient to guarantee successful prophylaxis in children.

There was also a consensus that children with inhibitors who have failed immune tolerance induction (ITI) or are not suitable candidates for this therapy should also be offered prophylaxis with by-passing agents. No such agreement was reached in relation to adults with inhibitors, largely because many of these would have already established joint damage. The cost of on-going treatment in adults would also be very high. More research is clearly needed in relation to the principal by-passing agents, FEIBA and NovoSeven. Two areas that the working group felt merited particular attention included development of a validated laboratory test for monitoring therapy as well as comparative head-to-head clinical studies.

The working group reaffirmed that single factor concentrates should be used wherever possible in rare bleeding disorders. It was noted that five new fibrinogen concentrates have recently been developed, as well as concentrates of factors V and X. Orphan drug designation for a factor concentrate should not be used to hinder the development, licensing and marketing of other products for the same condition that have demonstrably different protein modification or enhancement profiles. It was recognised that regulators have to follow legislation and do not have an entirely free hand in this regard. Pharmaceutical companies sometimes exploit the current position by requesting this protected status in order to secure market exclusivity for their products.

High-purity plasma-derived and recombinant von Willebrand factor concentrates will soon become available. Theoretical advantages over combined FVIII-VWF products include avoidance of accumulation of FVIII (which has been infrequently implicated in the development of venous thromboembolism after repeated treatment). The working group felt that these new products do not offer clear advantages over current products in routine clinical use, with the possible exceptions of elective surgery and prophylaxis, particularly in patients with recurrent gastrointestinal haemorrhage associated with angiodysplasia.

Organisation of haemophilia care is a very important issue. The working group approved the on-going work of the EUHANET project and agreed that a certification system for HTC's should be adopted by member states, based on common criteria, in order to improve standardisation of haemophilia care and to provide better access to services.

The working group also felt that a system of peer review external audits should be established in the longer term. In order to optimise the organisation of haemophilia care at a national level, the working group recommended that a formal body (such as a National Haemophilia Council) should be established in each country. This should include the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authority.

#### Principal conclusions and recommendations:

1. In order to optimise the organisation of haemophilia care nationally, it is recommended that a formal body be established in each country, including the relevant clinicians, national haemophilia patient organisation, health ministry, paying authority and (if appropriate) regulatory authority.

2. The minimum factor VIII consumption level in a country should be 3 IU/capita.
3. Decisions on whether to adopt a new product should not be based solely on cost.
4. Prophylaxis for children with severe haemophilia is already recognised as the optimum therapy. On-going prophylaxis for individual adults should also be provided when appropriate, based on a clinical decision made by the clinician in consultation with the patient.
5. Children with inhibitors who have failed immune tolerance induction (ITI) therapy, or who are not suitable for this treatment, should be offered prophylaxis with by-passing agents.
6. Single factor concentrates should be used as therapy wherever possible in patients with rare bleeding disorders.
7. Orphan drug designation for a factor concentrate should not be used to hinder the development, licensing and marketing of other products for the same condition that have demonstrably different protein modification or enhancement profiles.